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Original Research

Analysis of the nervus vagus effect on gastric adenocarcinoma development

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Abstract
Aim: In this study, we aimed to investigate whether there was an association between a change in the histological composition of the neuroelectrical activity of the vagal nerves and the gastric tumor.
Material and Methods: The pathological materials of patients who were operated on in our hospital with the diagnosis of gastric adenocarcinoma were analyzed retrospectively. Tumor cells, vagal nerve and tumor-invading nerve cells were photographed in successive sections at 4x, 10x, 20x and 40x magnifications for stereotypic counts. During the course of the vagal nerve, axon density per square millimeter and neuronal densities were counted. Statistical analysis was performed between the number of degenerated axons, VSI, axon thickness, and tumor stage by scoring according to the tumor size stage (Tumor 1-2-3-4:10).
Results: Twelve (44.4%) patients were female and 15 (55.6%) were male, with a mean age of 62.9 ± 7.7 years. As the tumor grade increased, the difference between the normal axon numbers was found to be significant. Likewise, as the tumor stage increased, there were significant differences between the number of degenerated axons and tumor stage, also there were significant differences between VSI and tumor stage, similarly. Tumor size and axon thickness differences were found to be significant.
Discussion: Increased electrical potentials lead to a decrease in apoptosis and an increase in tumorogenesis. In this context, vagal hyperactivity may cause gastric adenocarcinoma. Vagal nerves may become more degenerate in high-grade malignant tumors. Thus, it is concluded that vagal nerve weakness may contribute to the progression of tumors.

Keywords
Gastric Adenocarcinoma, Tumorogenesis, Vagal Nerve, Axon Density, Vasospasm Index

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Introduction

Gastric carcinoma is an insidious disease. It usually gives quite late symptoms and the symptoms are not specific to the disease. When it is caught in the early gastric cancer stage, the 5-year survival of this disease reaches 90% rates. For this reason, screening programs are being applied in some countries, such as Japan, where gastric carcinoma is common and early diagnosis success is achieved [1].

Multiple reasons play a role in the etiology of gastric cancer. While the majority of Helicobacter pylori infection contributes to cancer development, dietary features, lifestyle, obesity, smoking, genetics and other environmental features also play a role in the development of gastric cancer.

There is no primary tumor of the motor cortex and motor nerves of the brain. Tumors develop from the sensory cortex and sensory nerves. The failure of the autonomic nerves of the organs invites the inflammatory and tumoral process. Increasing electrical potentials causes a decrease in apoptosis and the development of tumogenesis. In this context, vagal hyperactivity can cause gastric adenocarcinoma. The nervous system regulates epithelial homeostasis in different ways, and this regulation by the nervous system partially involves the modulation (exchange) of stem cells and progenitor cells [2,3]. There is also a bilateral relationship between tumor cells and nerve cells such that tumors cause an activation of neurogenesis resulting in increased neuronal cell density in preneoplastic and neoplastic tissues. Also, activation of muscarinic receptors has been shown to promote cell transformation and cancer progression [4]. Recent studies have shown that surgical or pharmacological denervation suppresses gastric tumorigenesis. Denervation therapy has been effective in both early preneoplasia and late neoplasia/dysplasia. In the analysis of patients with gastric cancer, it has been shown that the risk of tumor in the vagotomized stomach is reduced and there is a correlation between more advanced tumors and increased innervation. It has been reported that no cancer is observed in the vagotomized part of the stomach in patients with unilateral vagotomy [5,6]. Our aim in this study is to investigate whether there is a relationship between gastric tumors and a change in histological composition that creates neuroelectric activity of vagal nerves in the development of gastric tumors.

Material and Methods

This study was approved by the Ethics Committee of Erzurum Atatürk University Faculty of Medicine (No: 2017/2-1-27). All procedures in this study involving human participants were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

All patients who underwent total gastrectomy with the diagnosis of gastric cancer between January 2010 and January 2017 at Atatürk University Faculty of Medicine General Surgery Service were retrospectively analyzed. While patients with pathological diagnosis of gastric adenocarcinoma were included in the study, tumors other than pathological adenocarcinoma were not included in the study. Patients with paraffin blocks of the vagal nerve, which were prepared and evaluated simultaneously with the examined tumor tissue, were included in the study. Thus, a total of 27 patients were included in the study group. All data were obtained from the hospital electronic archive system, patient files and preparations in the pathology department archive.

Changes in the nerve vagus that were taken in the simultaneous operation from patients who had undergone total gastrectomy for gastric adenocarcinoma were histopathologically compared with tumor cells. Tumor cells stained with hematoxylin--eosin dye and nerve cells located close to the tumor or with tumor invasion were photographed in sequential sections for stereotypic counting at 4x, 10x, 20x and 40x magnifications. Throughout the course of the vagal nerve, axon density per millimeter, number and neuron density of gastric ganglia were counted. The vasospasm index (VSI) was calculated in the gastric artery branch. The ratio of the radius of the vascular ring of the gastric artery end branch to the radius of the lumen area was accepted as the VSI. Similarly, for axon count in a normal vagal nerve, the total number of axons was found by completing the count of axons in an area of 45 degrees at a magnification of 10 in the light microscope, completing 360 degrees or multiplying by 8. In a case with a tumor, the number of axons in the damaged vagal nerve bundle was calculated in the same way.

Statistical analysis was performed between the number of degenerated axons, VSI, axon thickness, and tumor stage by scoring according to the tumor size stage (Tumor 1-2-3-4:10).

Results

Twenty-seven patients were included in the study, 12 (44.4%) were women and 15 (55.6%) were men. The average age was 62.9 ± 7.7 years, and the age of the patients ranged between 46 and 79. None of our patients have a family history; 11 of our patients (40.7%) had a history of smoking.

In 17 (62.9%) of our patients, no radiological findings were observed with radiological examinations. Wall thickening was detected in 4 (14.8%) gastric cardia, 2 (7.4%) small curvature, 3 (11.1%), gastroesophageal junction (GOJ), 1 (3.7%) large curvature, using computed tomography. In addition, liver

Table 1. Patients Characteristics and demographic features

	n: 27
Age	62,93±7,76
Gender	
Female	12 (%44,4)
Male	15 (%55,6)
Endoscopy Findings	
Curvature Major	2 (%7,4)
Cardia	18 (%66,7)
Curvature Minor	7 (%25,9)
Radiology Findings	
Curvature Major	1 (% 3,7)
Gastroesophageal Junction	3 (%11,1)
Liver Metastasis	2 (%7,4)
Cardia Wall Thickness	4 (%14,8)
Curvature Minor	2 (%7,4)
Normal radiologic findings	15 (%55,6)
Pathology	
Mucinous adenocarcinoma	4 (%14,8)
Neuroendocrine differentiation adenocarcinoma	1 (%3,7)

metastasis was detected in 2 (7.4%) of the cases, and total gastrectomy was performed because of the presence of obstruction in these patients. In the preoperative endoscopy, 66.6% of the cases were detected in cardia, 25.9% in small curvature, 7.4% in large curvature

Table 2. Neuropathological Analysis

	T 1-2 tumors	T 3-4 tumors	P value
VS normal axon count (n/mm²)	34.23±4.32	21.54±3.94	< 0.001
VS degenerated axon (n/mm²)	245±34	11.87±1.23	<0.001
*GAB VSI²	0.43±0.034	3.85±0.76	<0.005
Vagal axon thickness (µm)	>2.3±0.95	<1.8±0.07	<0.001
Tumor Scale Score (0-10)	<4	>6	

*GAB: Gastric Artery Branch

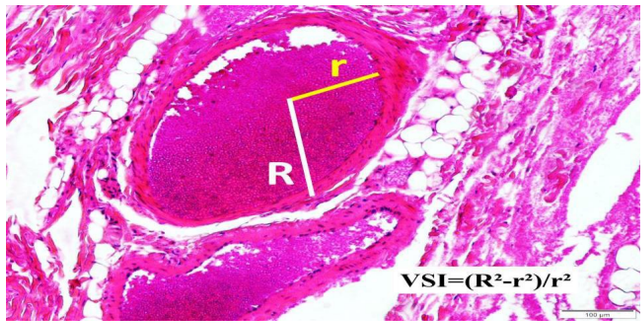

Figure 1. Calculating of VSI (IM, H-E x10)

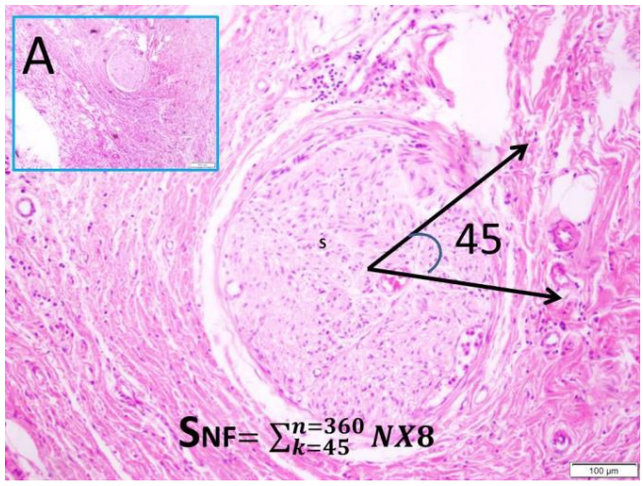

Figure 2. Calculation of the total number of axons (IM, H-E x10)

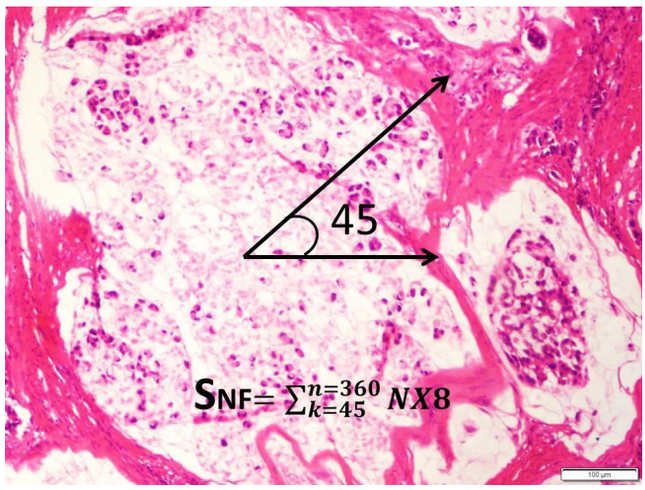

Figure 3. Damaged vagal nerve bundle in the case with tumor (IM, H-E x10)

In our analysis according to the pathology result, all cases were adenocarcinoma, and 4 (14.8%) had sub-type mucinous adenocarcinoma, 1 (3.84%) of our patients had early gastric carcinoma and 1 (3.7%) of our patients had neuroendocrine differentiation in adenocarcinoma. In 22.2% of our cases, there were various rates of mucinous components. In addition, perineural invasion was present in 48.1% of cases (Table 1).

Neuropathological Results

Statistical data were compared using the Mann-Witney U test by counting the number of normal and degenerated axons per mm² of the vagal nerves, measuring the vagal axon thickness, calculating the vasospasm index values (VSI) of the gastric artery branches and tumor scale scores in preparations containing the vagal nerve and gastric artery branches that were photographed stereotypically in gastric adenocancer cases (Figures 1, 2 and 3).

The normal number of axons in the vagal nerve in low-stage tumors was 34,234±4.320 per square millimeter, while it was 21,543±3.943 per square millimeter in high-stage tumors. A statistically significant difference was found between tumor size and normal axon numbers (p<0.001). Therefore, a higher number of healthy axons in the vagal nerve may result in smaller tumor size and lower stage. In addition, the number of degenerated axons per square millimeter in the vagal nerve was 245±34 in low-stage tumors, and 11.876±1.234 n/mm² in patients with high tumor size. The difference in numbers was found to be statistically significant (p<0.001) (Table 2).

Vagal axon thickness was >2.3±0.95µm in T1-2 tumors and <1.8±0.07 µm in T3-4 tumors. Here, too, a significant difference was found, indicating that the tumor size will increase as the axon thickness increases (p <0.001). The VSI in the gastric artery branches was 0.432±0.034 in low-stage T 1-2 tumors and 3.850±0.76 in T 3-4 tumors. This was also found to be statistically significant (p<0.005) (Table 2).

Discussion

Gastric cancer is the most common type of cancer after lung prostate, vesical and colorectal cancer in men and after breast, thyroid, colorectal, uterus and lung cancer in women [3]. Gastric carcinoma is an insidious disease. It usually gives quite late symptoms and the symptoms are not specific to the disease. When it is caught in the early gastric cancer stage, the 5-year survival of this disease reaches 90% rates. For this reason, screening programs are applied in some countries, such as Japan, where gastric carcinoma is common and early diagnosis success is achieved [1]. Although multiple causes play a role in the etiology of gastric cancer, the number of studies in the literature about the effect of nervus vagus, which is important in gastric innervation, on cancer development, is insufficient. Our aim in this study was to observe the relationship between the stage of the tumor and nerve damage. Thus, it was necessary to reveal whether nerve damage was involved in the tumor development process and tumor progression process. It is thought that vagal weakness may play a role in gastric cancers [7]. In lung cancers, it is claimed that nicotine leads to cancer development by blocking nicotinic receptors and reducing the electrical resistance of the vagal nerves in the lung

[8,9]. Therefore, it is thought that the same mechanism may also induce gastric cancer.

There are publications that congenital weakness of the vagal nerve or tumoral invasion may cause cancer formation by weakening gastric immunity or may cause further progression of existing cancer [10]. In addition, it was thought that vagal nerves may affect mood [11]. Therefore, in people with pessimistic personality, the vagal nerve may be weaker, and gastrointestinal immunity may be weak. Thus, this situation may induce gastrointestinal tumorogenesis. In the study on the effect of bilateral or unilateral vagotomy on gastric carcinogenesis published by Tatsuta et al. in 1988, vagotomy has been reported to have a promoting effect on gastric carcinogenesis [12]. In a study published in 2014 by Zhao et al., it was stated that vagal innervation contributes to gastric tumorigenesis, and denervation is a viable strategy for stomach cancer control [5]. In our study, when we investigated the relationship between axon numbers and tumor, we found that the number of degenerated axons was high in cases where the tumor size stage was advanced. In addition, when we compared axon thickness and tumor size, we concluded that lower grade tumors had greater axon thickness. Accordingly, it was concluded that vagal nerve conduction would be better in lower grade tumors, and vagal nerve conduction would be worse as axon thickness decreased in higher-grade tumors. We conclude that vagal nerve damage may cause tumor progression or the vagal nerves may become more degenerated in high-grade malignant tumors.

In a study published by Mozsik et al., the possible mechanisms of the vagal nerve were examined in the development of gastric mucosal defense, and after vagotomy, it has been identified that protective factors on the gastric mucosa decreased and mucosal damage increased [13]. Based on this, gastrointestinal bleeding may be higher in vagal nerve injuries. In our study, when VSI differences were compared according to tumor size, they were found statistically significant. Thus, it was thought that vagal nerve damage in malignant tumors with a higher grade according to tumor size causes more vasoconstriction in the gastric arteries, which can lead to tumor necrosis by disrupting tumor nutrition. While the invasion of the vagal nerves is in favor of the tumor, it can be interpreted as an advantage considering that the tumor may shrink to the necrosis as a result of denervation and vasospasm of the arteries feeding the tumor. In addition, it was thought that the arteries that had advanced spasms due to increased VSI with vagal nerve damage could be ruptured.

We could not perform a statistical study because we could not access enough parasympathetic ganglion data for statistics, but it may be considered responsible for gastric carcinomas with mucinous and hypersecretion. We have collected data on the presence of more parasympathetic ganglia in some mucinous cancers. Studies on this subject can be done in the coming years. Although there are not enough studies in the literature about the effect of the vagal nerve on gastric carcinogenesis, we anticipate that the effect of the vagal nerve on gastric adenocarcinoma can be revealed with future studies.

To the best of our knowledge, this is the first study in the literature in terms of histopathological examination of the effect of vagal nerve on gastric adenocarcinoma. The small number of patients and the retrospective nature of our study are limitations. Nevertheless, although there is not enough study in the literature on the effect of the vagal nerve on gastric carcinogenesis, we predict that this study may guide for studies to be carried out in the coming years.

Conclusion

Vagal nerves may become more degenerate in high-grade malignant tumors. Consequently, vagal nerve weakness may contribute to the progression of tumors. Thus, we think that vagal nerve degeneration may be a poor prognostic marker in the coming years.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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